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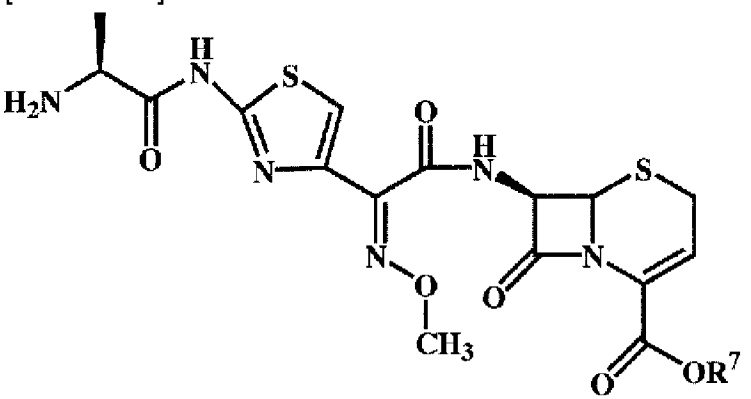
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

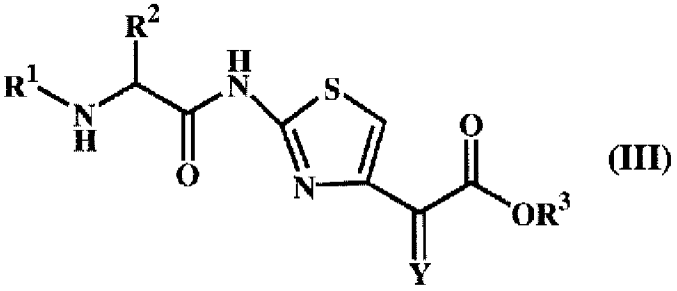
[Detailed Description of the Invention]
[0001]
[Field of the Invention]This invention relates to the method of manufacturing an amide thiazole derivative ester compound from N-protection amino acid compound and an aminothiazole derivative ester compound.
[0002]
[Description of the Prior Art]An aminothiazole derivative is a compound useful as an intermediate of drugs manufacture.
It is an important compound used as a side chain of antibiotics, such as cephalosporin.
For example, when an aminothiazole derivative combines with beta-lactam system compounds, such as 7-aminocephalosporanic acid, by an amidation reaction, the basic skeleton of the antibiotic is made.
[0003]They generally have a broad antimicrobial spectrum, and since cephalosporins antibiotics also have few side effects, they are antibiotics which attract attention. However, the aminothiazole derivative and the cephalosporin derivative compounded from beta-lactam system compound generally had the problem that gastrointestinal absorption nature was bad. Then, by making the amino group of an aminothiazole derivative react to the intermediate and beta-lactam system compound which are produced by protecting with a compound like the amino acid cut easily with an enzyme in the living body like peptidase, etc., The art of obtaining the high cephalosporin derivative (it is also called a prodrug type cephalosporin derivative.) of gastrointestinal absorption nature is developed.
[0004]As such a prodrug type cephalosporin derivative, it is following formula (IV).
[0005]
[Formula 4]



(IV)

[0006](R^7 is 1-alkanoloxy alkyl group or 1-alkoxycarbonyloxyalkyl group among a formula.) -- the prodrug type cephalosporin derivative shown is known.
The demand of these derivatives is increasing increasingly from the goodness of the gastrointestinal absorption nature.

[0007]For this reason, following formula (III) which is an important intermediate of the above-mentioned prodrug type cephalosporin derivative
[0008]
[Formula 5]



(III)

[0009]{R^1 is a protective group of an amino group among a formula, and R^2 A hydrogen atom, They are a saturated hydrocarbon group of the carbon numbers 1-6, or an unsaturated hydrocarbon group of the carbon numbers 2-10, R^3 is an alkyl group of the carbon numbers 1-7, or an aralkyl group of the carbon numbers 7-11, Y -- following formula =N-R^4 or =CH-R^5 (inside of formula, and R^4 -- the alkyloxy group of the carbon numbers 1-7.) Are an aralkyloxy group of the carbon numbers 7-19, and R^5 Or a hydrogen atom, They are an alkyl group of the carbon numbers 1-7, an aralkyl group of the carbon numbers 7-19, an alkyloxy group of the carbon numbers 1-7, or an aralkyloxy group of the carbon numbers 7-19. They are two hydrogen atoms combined with a carbon atom by the divalent basis shown or a single bond. It is important to manufacture the amide thiazole derivative ester compound shown by} with sufficient yield by a high grade. About this amide thiazole derivative ester compound, what has high optical purity is desired from the relation with the use.
[0010]As a synthesizing method of this amide thiazole derivative ester compound, ** After making N-protection amino acid compound react to N-imide hydroxysuccinate under existence of the dicyclohexylcarbodiimide as a condensing agent and compounding a succinimid object, It is made to react to an aminothiazole derivative ester compound furthermore, and is 112.4% (calculated value based on a value given in document.) of isolation yield about an amide thiazole derivative ester compound. It seems that what isolated at this time contains the impurity since yield is over 100%. How to compound (JP,S58-180491,A), And a **N-protection amino acid compound and an aminothiazole derivative ester compound under existence of 4-dimethylaminopyridine, It is made to react to the 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride which is a water-soluble carbodiimide as a condensing agent, and the method (JP,H3-204883,A) of compounding an amide thiazole derivative ester compound with 67.5% of isolation yield is known.
[0011]
[Problem(s) to be Solved by the Invention]However, in the method indicated to above-mentioned JP,S58-180491,A. When a succinimid object is made to compound using dicyclohexylcarbodiimide from N-tert-carbobutoxy-L-alanine and N-imide hydroxysuccinate, in order that a poorly soluble urea object may carry out

a byproduction, After filtering this, it is necessary to make it react to 2-(2-aminothiazole 4-yl)-2-methoxy imino acetic acid methyl ester, and there is a problem that a process is complicated. Isolation yield 112.4% (calculated value based on a value given in document), It seems that the thing which isolated at this time contains the impurity since yield is over 100%, and it is predicted from the isolation yield after the next process which advances still more quantitatively being 69.3% that true condensation yield was about 70% of low value.

[0012]In the method indicated to above-mentioned JP,H3-204883,A. The isolation yield of the amide thiazole derivative ester compound which is an object was as low as about 67.5%, and there was a problem that a water-soluble urea object carried out a byproduction, as a by-product which what does not need to be removed in the middle of a reaction must remove eventually.

[0013]Thus, the method of manufacturing the amide thiazole derivative ester compound shown by said (III) formula, especially this amide thiazole derivative ester compound with high optical purity with a high grade and high yield is not learned, but development of such a method is desired.

[0014]

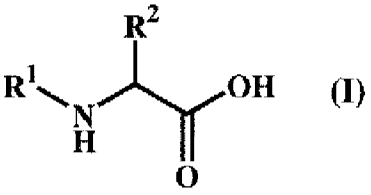
[Means for Solving the Problem]This invention persons examined a reaction mechanism of an above-mentioned conventional method first in view of this actual condition. As a result, when carbodiimide system condensing agents, such as dicyclohexylcarbodiimide and a 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, are used. There was a reaction path which goes via an acid anhydride of N-protection amino acid compound as one of the reaction paths, and since the reaction of this acid anhydride and an aminothiazole derivative ester compound was very slow, it traced that yield was low.

[0015]And a place which examined many things about a condensing agent which advances a reaction based on this knowledge without going via the above reactant low acid anhydrides, Under existence of the third class amine compound, without carrying out the byproduction of the urea object with difficult removal, etc. by using a carboxylic acid halide compound as a condensing agent, it finds out that an object is obtained with high yield, and came to complete this invention.

[0016]That is, this invention is following general formula (I).

[0017]

[Formula 6]

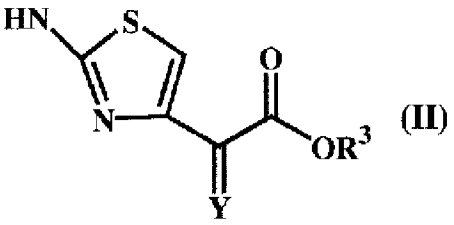


(I)

[0018](R^1 is a protective group of an amino group among a formula, and R^2 is a hydrogen atom, a saturated hydrocarbon group of the carbon numbers 1-6, or an unsaturated hydrocarbon group of the carbon numbers 2-10.) -- N-protection amino acid compound shown and following general formula (II)

[0019]

[Formula 7]

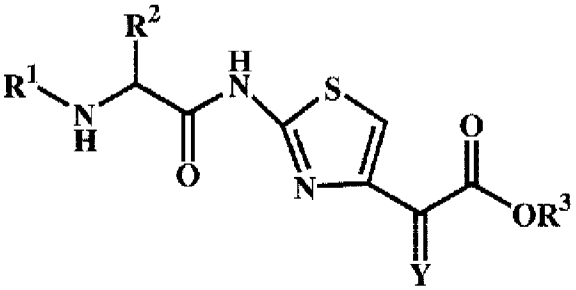


(II)

[0020]{R^3 is an alkyl group of the carbon numbers 1-7, or an aralkyl group of the carbon numbers 7-11 among a formula, Y -- following formula =N-R^4 or =CH-R^5 (inside of formula, and R^4 -- the alkyloxy group of the carbon numbers 1-7.) Are an aralkyloxy group of the carbon numbers 7-19, and R^5 Or a hydrogen atom, They are an alkyl group of the carbon numbers 1-7, an aralkyl group of the carbon numbers 7-19, an alkyloxy group of the carbon numbers 1-7, or an aralkyloxy group of the carbon numbers 7-19. They are two hydrogen atoms combined with a carbon atom by the divalent basis shown or a single bond. The aminothiazole derivative ester compound shown by} is made to condense using a condensing agent, and it is following general formula (III).

[0021]

[Formula 8]



(III)

[0022]{Among a formula, R^1 and R^2 are synonymous with R^1 and R^2 in said general formula (I) respectively, and R^3 and their Y are synonymous with R^3 and Y in said general formula (II) respectively. In the method of manufacturing the amide thiazole derivative ester compound shown by}, it is a manufacturing method of said amide thiazole derivative ester compound using a carboxylic acid halide compound combining the third class amine compound as a condensing agent.

[0023]Although it is known that a carboxylic acid halide compound can use it as a condensing agent, the example used for the condensation reaction using an aminothiazole derivative ester compound like this invention is not known. This is considered for an aminothiazole derivative ester compound to isomerize by the hydrogen halide which carries out a byproduction when a carboxylic acid halide compound is used as a condensing agent.

[0024]This invention by using a carboxylic acid halide compound combining the third class amine compound, Generation of reactant low N-protection amino acid anhydride is controlled, and the target amide thiazole derivative ester compound is manufactured with high yield which was not able to be realized by a conventional method at the same time it controls isomerization of an aminothiazole derivative ester compound.

[0025]

[Embodiment of the Invention]N-protection amino acid compound in which the manufacturing method of this invention is shown by said general formula (I). (it is also only hereafter called "raw material N-protection amino acid".) -- it is shown by said general formula (II) -- an aminothiazole derivative ester compound. (It is also only hereafter called "raw material aminothiazole derivative ester".) It is made to condense, When manufacturing

the amide thiazole derivative ester compound shown by said general formula (III), it is characterized [greatest] by using a carboxylic acid halide compound combining the third class amine compound as a condensing agent.

[0026]Even if a direct reaction agent does not react in this invention as well as the compound which the condensing agent refers to the compound which has the operation which promotes a condensation reaction, and the compound itself [this] reacts to a reaction agent, and forms an activity intermediate, the compound which makes a condensation reaction advance effectively as a result by a certain operation is said.

[0027]Especially if the carboxylic acid halide compound used by this invention is an acid halide compound of the organic compound which has a carboxyl group, it will not be limited, but it can use a publicly known carboxylic acid halide compound.

[0028]If the carboxylic acid halide compound which can be conveniently used in this invention is illustrated concretely, an acetyl flora -- ide, acetyl chloride, an acetyl star's picture, and an acetyl iodide. a propionic acid flora -- ide, propionyl chloride, and a propionic acid star's picture. iodination propionyl and a pivaloyl flora -- ide and a pivaloyl chloride. a pivaloyl star's picture, iodination pivaloyl, and an isovaleroyl flora -- ide. saturated-carboxylic-acid halide compound; acrylic acid floras, such as isovaleroyl chloride and iodination isovaleroyl, -- ide. Acrylic acid chloride, an acrylic acid star's picture, iodination acryloyl, a methacrylic acid flora -- ide, methacrylic acid chloride, and a methacrylic acid star's picture. unsaturated-carboxylic-acid halide compound [, such as iodination methacryloyl,]; -- a benzoyl flora -- ide. benzoyl chloride, a benzoyl star's picture, iodination benzoyl, and a toluoyl flora -- ide. toluoyl chloride, a toluoyl star's picture, iodination toluoyl, and a naphthoyl flora -- aromatic-carboxylic-acid halide compounds, such as ide, naphthoyl chloride, and a naphthoyl star's picture, etc. can be mentioned.

[0029]the inside of these -- especially -- the propionic acid flora from the height of a condensation inversion rate, and the ease of handling -- ide. propionyl chloride, a propionic acid star's picture, and a pivaloyl flora -- ide. saturated-carboxylic-acid halide compound; benzoyl floras, such as a pivaloyl chloride and a pivaloyl star's picture, -- ide. benzoyl chloride, a benzoyl star's picture, and a toluoyl flora -- ide, toluoyl chloride, a toluoyl star's picture, and a naphthoyl flora -- aromatic-carboxylic-acid halide compounds, such as ide, naphthoyl chloride, and a naphthoyl star's picture, etc. can use conveniently. Saturated-carboxylic-acid halide compounds, such as the little of a by-product to a pivaloyl chloride; aromatic-carboxylic-acid halide compounds, such as toluoyl chloride and naphthoyl chloride, etc. can use conveniently especially.

[0030]What came to hand as a reagent and an industrial source can be used for them after these carboxylic acid halide compounds refine recrystallization, distillation, etc. remaining as it is or if needed. The carboxylic acid halide compound which cannot be obtained is compoundable as follows. Namely, carboxylic acid fluoride is compoundable by making a cyanuric fluoride react to carboxylic acid, A carboxylate ghost is compoundable by making a thionyl chloride react to carboxylic acid, A carboxylic acid bromide can be compounded by making dibromotriphenylphosphorane react to carboxylic acid, and a carboxylic acid iodide can be easily compounded by making sodium iodide react to a carboxylate ghost. The compound carboxylic acid halide compound can use the compound thing, after refining recrystallization, distillation, etc. remaining as it is or if needed.

[0031]Although the amount in particular of these carboxylic acid halide compound used is not restricted, Since the by-product in which the carboxylic acid halide compound carried out the direct reaction to raw material aminothiazole derivative ester will increase if too large [if too small, an unreacted raw material will remain, and], it is preferred to use in 0.5-5 mol to 1 mol of raw material N-protection amino acid. Considering obtaining

the object of a high grade, especially the thing used in 0.8-3 mol to 1 mol of raw material N-protection amino acid is preferred.

[0032]In this invention, as the third class amine compound used together with the above-mentioned carboxylic acid halide compound, especially if it has the operation which catches hydrogen halide, it will not be limited, but the publicly known third class amine compound can be used. If this Tokikazu class or the second class amine is used, in order that the by-product reacted to raw material N-protection amino acid, the first class, or the second class amine compound may generate, the amine which can be used is limited to the third class amine compound. When the third class amine compound which can be used by this invention is illustrated concretely, trimethylamine, Triethylamine, tri-n-propylamine, tri-n-butylamine, The third class of aliphatic series amine compound;N-methylpyrrolidines, such as diisopropylmethylamine and diisopropylethylamine, N-methyl piperidine, N-ethylpiperidine, N-methyl morpholine, The third class of annular amine compounds, such as N-ethyl morpholine; Pyridine, N,N-dimethylamino pyridine, The third class of annular unsaturated hydrocarbon amine compound;N,N, such as N-methylpyrrole, -N',N'-tetramethylethylenediamine, N,N,N',N'-tetraethyl ethylenediamine, N,N,N',N'-tetramethylethylenediamine, N,N,N',N' - tetramethyl one -- 1,3 - propylenediamine -- N,N,N',N' - tetramethyl one -- 1,3 - butanediamine -- N -- N -- N -- ' -- N -- ' - tetramethyl one -- 1,4-butanediamine -- etc. -- aliphatic series -- three -- class -- a diamine compound -- etc. -- it can mention .

[0033]Also especially in these, trimethylamine from the height of a condensation inversion rate, triethylamine, Tri-n-propylamine, tri-n-butylamine, diisopropylmethylamine, The third class of annular amine compounds, such as the third class of aliphatic series amine compound [, such as diisopropylethylamine,]; or N-methylpyrrolidine, N-methyl piperidine, N-ethylpiperidine, N-methyl morpholine, and N-ethyl morpholine, are used suitably. It is available as a reagent and an industrial source, and after all of the third class amine compounds of these refine recrystallization, distillation, etc. remaining as it is or if needed, they can use what came to hand.

[0034]Although the amount in particular of the above-mentioned third class amine compound used is not restricted, if too small, a condensation reaction neither not progressing nor hydrogen halide capturing capacity can fall, raw material aminothiazole derivative ester cannot isomerize, and an object with high optical purity cannot be obtained with high yield. Since a carboxylic acid halide compound will be disassembled and a condensation inversion rate will fall if too large, it is preferred to use in 0.5-5.0 mol to 1 mol of carboxylic acid halide compounds to be used. Especially the thing used in 0.7-1.3 mol to 1 mol of carboxylic acid halide compounds to be used from a viewpoint of reducing impurities, such as an unreacted raw material and a decomposition by-product, and obtaining the object of a high grade is preferred.

[0035]In the manufacturing method of this invention, except using said carboxylic acid halide compound combining the third class amine compound as a condensing agent, As N-protection amino acid compound which the method of manufacturing the conventional N-protection amide thiazole ester derivative compound, and the changing place in particular do not have, and serves as a raw material, and an aminothiazole ester derivative, what is used with the conventional method can use it without restriction.

[0036]That is, as an N-protection amino acid compound, the raw material N-protection amino acid shown by said general formula (I) can be used. R^1 in said general formula (I) is a protective group of an amino group. This R^1 is not what will be restricted especially if it is an organic residue which has the operation which protects an amino group, If the basis which has such an operation is illustrated concretely, a formyl group, an

acetyl group, Acyl type protective groups, such as a chloroacetyl group and acetoacetyl groups; An isopropoxycarbonyl group, Alkoxycarbonyl groups, such as a tert-butoxycarbonyl group; aralkyl groups, such as aralkyloxy carbonyl group; benzyls, such as a benzyloxycarbonyl group and 9-fluorenyl methoxycarbonyl group, and a triphenylmethyl group, etc. can be mentioned.

[0037]Also especially in these, from a point of the racemization depressor effect at the time of a condensation reaction to an isopropoxycarbonyl group. It is preferred to use aralkyloxy carbonyl groups, such as alkoxycarbonyl group [, such as a tert-butoxycarbonyl group,]; or a benzyloxycarbonyl group, and 9-fluorenyl methoxycarbonyl group. It is most preferred to use a tert-butoxycarbonyl group from the ease of deprotection furthermore.

[0038]R^2 in said general formula (I) is a hydrogen atom, a saturated hydrocarbon group of the carbon numbers 1-6, or an unsaturated hydrocarbon group of the carbon numbers 2-10. The saturated hydrocarbon group of the carbon numbers 1-6 may have branching also by straight chain shape. As this saturated hydrocarbon group, the alkyl group of the carbon numbers 1-6 is preferred, and if such an alkyl group is illustrated concretely, a methyl group, an ethyl group, an isopropyl group, 2-methylpropyl group, 1-methylpropyl group, etc. will be illustrated.

[0039]As an unsaturated hydrocarbon group of the carbon numbers 2-10, benzyl, a phenethyl group, 1-phenylethyl group, a phenyl group, a naphthyl group, etc. are illustrated.

[0040]Since the absorptivity and the biodegradation characteristic at the time of using a prodrug type cephalosporin derivative eventually are good as R^2 also in these, it is preferred that it is especially a methyl group.

[0041]If the raw material N-protection amino acid which can be used in this invention is illustrated concretely, N-acetylglycine, N-acetylalanine, N-acetyl valine, Acylamino acid compound;tert-butoxycarbonylglycines, such as N-acetylleucine, N-acetyl phenylglycine, and N-acetylphenylalanine, A tert-butoxycarbonylalanine, tert-butoxycarbonyl valine, tert-butoxycarbonylleucine, tert-butoxycarbonyl phenylglycine, Alkoxycarbonylamino acid compounds, such as tert-butoxycarbonylphenylalanine; N-benzyloxycarbonyl glycine, N-benzyloxycarbonyl alanine, N-benzyloxycarbonyl valine, N-benzyloxycarbonyl leucine, N-benzyloxycarbonyl phenylalanine, N-(9-fluorenyl carbomethoxy) glycine, N-(9-fluorenyl carbomethoxy) alanine, N-(9-fluorenyl carbomethoxy) valine, N-(9-fluorenyl carbomethoxy) leucine, Aralkyloxy carbonylamino acid compounds, such as N-(9-fluorenyl carbomethoxy) phenylalanine; N-benzylglycine, N-benzylalanine, N-benzyl valine, N-benzylleucine, N-benzylphenyl glycine, N-benzylphenyl alanine, N-triphenylmethylglycine, N-triphenylmethylalanine, N-triphenylmethyl valine, Aralkyl amino acid compounds, such as N-triphenylmethylleucine, N-triphenylmethylalanine, N-triphenylmethyl phenylglycine, and N-triphenylmethylphenylalanine, etc. can be mentioned.

[0042]Also especially in these, from the high level of the racemization control ability at the time of a condensation reaction to a tert-butoxycarbonylalanine. tert-butoxycarbonyl valine, tert-butoxycarbonylleucine, Alkoxycarbonylamino acid compound; or N-benzyloxycarbonyl alanines, such as tert-butoxycarbonyl phenylglycine and tert-butoxycarbonylphenylalanine, N-benzyloxycarbonyl valine, N-benzyloxycarbonyl leucine, N-benzyloxycarbonyl phenylglycine, N-benzyloxycarbonyl phenylalanine, N-(9-fluorenyl carbomethoxy) glycine, N-(9-fluorenyl carbomethoxy) alanine, It is preferred to use aralkyloxy carbonylamino acid compounds, such as N-(9-fluorenyl carbomethoxy) valine, N-(9-fluorenyl carbomethoxy) leucine, and N-

(9-fluorenyl carbomethoxy) phenylalanine. From the ease of protection and a deprotection reaction to a tert-butoxycarbonylalanine. Especially that of **** for tert-butoxycarbonylamino acid compounds, such as tert-butoxycarbonyl valine, tert-butoxycarbonylleucine, tert-butoxycarbonyl phenylglycine, and tert-butoxycarbonylphenylalanine, is preferred.

[0043]Although it is available also as a reagent or an industrial source, these raw material N-protection amino acid can be compounded when it cannot obtain. That is, it is easily compoundable by making a protecting agent react to corresponding amino acid under base existence.

[0044]A thing with asymmetrical carbon is also in these raw material N-protection amino acid. Although it is usable in any N-protection amino acid compound of L object and D object in this invention, L object is suitably used from a point of the pharmacological activity of a final product.

[0045]As an aminothiazole derivative ester compound which is another raw material compound used by this invention, raw material amino ** shown by said general formula (II) can be used. R^3 in said general formula (II) is an alkyl group of the carbon numbers 1-7, or an aralkyl group of the carbon numbers 7-11. The alkyl group of the carbon numbers 1-7 may have branching also by straight chain shape, and a methyl group, an ethyl group, n-propyl group, an isopropyl group, n-butyl group, a sec-butyl group, a tert-butyl group, etc. are mentioned as these alkyl groups. Benzyl, a naphthyl methyl group, etc. are mentioned as an aralkyl group of the carbon numbers 7-11. Also in these, since the operation in connection with next hydrolysis is easy as R^3, it is preferred that they are especially a methyl group or an ethyl group.

[0046]Y in said general formula (II) is two hydrogen atoms combined with the carbon atom which Y combines by the divalent basis shown by following formula =N-R^4 or =CHR^5, or a single bond.

[0047]R^4 in the above-mentioned formula is an alkyloxy group of the carbon numbers 1-7, or an aralkyloxy group of the carbon numbers 7-19. The alkyloxy group of the carbon numbers 1-7 may have branching also by straight chain shape, and, specifically, a methoxy group, an ethoxy basis, a propyloxy group, an isopropyloxy group, n-butyloxy group, a sec-butyloxy group, a tert-butyloxy group, etc. are illustrated. A benzyloxy group, a triphenylmethyloxy group, etc. are illustrated as an aralkyloxy group of the carbon numbers 7-19.

[0048]R^5 in the above-mentioned formula is a hydrogen atom, an alkyl group of the carbon numbers 1-7, an aralkyl group of the carbon numbers 7-19, an alkyloxy group of the carbon numbers 1-7, or an aralkyloxy group of the carbon numbers 7-19. The thing same as an alkyl group of the carbon numbers 1-7 as the thing in R^3 is mentioned. Benzyl, a triphenylmethyl group, etc. are illustrated as an aralkyl group of the carbon numbers 7-19. The thing respectively same as the alkyloxy group of the carbon numbers 1-7 and an aralkyloxy group of the carbon numbers 7-19 as the thing in R^4 is mentioned.

[0049]When Y is two hydrogen atoms combined with a carbon atom by a single bond, the basis shown by -C(=Y)- in said general formula (II) turns into a -CH_2-basis.

[0050]If the raw material aminothiazole derivative ester which can be used in this invention is illustrated concretely, 2 -(2-aminothiazole 4-yl)- Methyl acetate, 2-(2-aminothiazole 4-yl) ethyl acetate, 2-(2-aminothiazole 4-yl)-2-methoxy imino methyl acetate, 2-(2-aminothiazole 4-yl)-2-methoxyimino ethyl acetate, 2-(2-aminothiazole 4-yl)-2-methoxy imino acetic acid tert-butyl, 2-(2-aminothiazole 4-yl)-2-methoxy imino benzyl acetate, 2-(2-aminothiazole 4-yl)-2-ethoxy imino methyl acetate, 2-(2-aminothiazole 4-yl)-2-ethoxy imino ethyl acetate, 2-(2-aminothiazole 4-yl)-2-ethoxy imino benzyl acetate, 2-(2-aminothiazole 4-yl)-2-benzyloxy imino

ethyl acetate, 2-(2-aminothiazole 4-yl)-2-triphenyloxy imino ethyl acetate, 2-(2-aminothiazole 4-yl)-2-triphenyloxy imino benzyl acetate, 2-(2-aminothiazole 4-yl)-2-ethyl propenoate, 2-(2-aminothiazole 4-yl)-2-butene acid ethyl, 2-(2-aminothiazole 4-yl)-2-pentene acid ethyl, etc. can be mentioned.

[0051]Also in these, from the height of the effect of a prodrug type cephalosporin derivative. 2-(2-aminothiazole 4-yl)-2-methoxy imino acetic acid methyl ester, 2-(2-aminothiazole 4-yl)-2-methoxyimino-ethyl-acetate ester, etc. are used especially suitably.

[0052]Although it is available as a reagent or an industrial source, these raw material aminothiazole derivative ester can be compounded as follows, when it cannot obtain. Namely, alkoxy imino acetic acid compounds are compoundable by making the ester compound, alkyl halide, or aralkyl halide of corresponding 2-(2-aminothiazole 4-yl)-2-hydroxy imino acetic acid react, Alkene acid compounds are easily compoundable by making it react to thiourea, after making the aldehyde corresponding to the ester compound of corresponding 4-chloroacetoacetic acid react and obtaining a 4-chloro-2-alkylidene acetoacetic ester compound.

[0053]E object and the isomer of Z body may exist, and in this invention, although it is usable in both E object and Z body, Z body is suitably used for raw material aminothiazole derivative ester from a point of the pharmacological activity of a final product.

[0054]The amount of the above-mentioned raw material aminothiazole derivative ester used, Although not restricted in particular, if too large [if too small, unreacted raw material N-protection amino acid will remain, and], in order that raw material aminothiazole derivative ester may be unreacted and may remain, it is preferred to use in 0.5-5 mol to 1 mol of raw material N-protection amino acid. It is preferred especially to use from a viewpoint that the amide thiazole derivative ester compound of a high grade is obtained, in 0.8-2 mol to 1 mol of raw material N-protection amino acid.

[0055]In the manufacturing method of this invention, in order to react uniformly for a short time that it is easy to control a reaction condition, it is preferred to use a solvent when reacting. When the solvent which can be used by this invention is illustrated concretely, n-pentane, n-hexane, Saturated hydrocarbon, such as n-heptane, cyclopentane, and cyclohexane; Benzene, Unsaturated hydrocarbon, such as toluene and xylene, a methylene chloride, chloroform, Halogenated hydrocarbon, such as a carbon tetrachloride; Diethylether, diisopropyl ether, Ether, such as tert-butylmethyl ether, a tetrahydrofuran, and 1,4-dioxane; Ethyl acetate, Methyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, Ester species, such as acetic acid tert-butyl; Acetone, methyl ethyl ketone, Ketone, such as methyl isobutyl ketone; Carbonate; acetonitrile, such as dimethyl carbonate and diethyl carbonate, Amide, such as nitril, such as propionitrile, N.N-dimethylformamide, and N,N-dimethylacetamide; alcohols, such as sulfoxide;tert-butyl alcohol, such as dimethyl sulfoxide, etc. can be mentioned.

[0056]Also in these solvents, halogenated hydrocarbon, ether, ester species, ketone, or carbonate is suitably used from the height of condensation yield. It is preferred that specific inductive capacity, such as diethylether, JIISO pro yl ether, chloroform, ethyl acetate, and a tetrahydrofuran, especially uses 20 or less solvent from a viewpoint of preventing racemization from happening, during a reaction.

[0057]Although the amount in particular of these solvents used is not restricted, it is preferred to use from viewpoints of the ease of reaction control, economical efficiency, etc. in the range of 100 to 1000 weight section especially 50 to 10000 weight section to raw material N-protection amino acid 100 weight section.

[0058]The operating procedure in the manufacturing method of this invention will not be limited especially if the carboxylic acid halide compound as a condensing agent is used combining the third class amine compound,

but it may add all the ingredients simultaneously also about the addition method of each reaction agent, may shift time and may add each ingredient independently. However, the reaction in this invention is an exoergic reaction, and when the cooling capability of the system of reaction is exceeded greatly, the system of reaction serves as an elevated temperature, Since raw materials and reaction intermediates, such as raw material N-protection amino acid and a carboxylic acid halide compound, decompose or a side reaction occurs easily, it is preferred to control an addition order and an adding speed so that reaction temperature can be adjusted within suitable limits in consideration of the cooling capability of the system of reaction.

[0059]When a reaction scale is small-scale, first For example, raw material N-protection amino acid and the third class amine compound, The carboxylic acid halide compound which is a hyperactive compound into the mixture obtained by furthermore mixing a solvent if needed, Add adjusting reaction temperature and the resultant (namely, reaction intermediate) of a carboxylic acid halide compound and a raw material N-protection amino acid compound is made to generate, Reaction temperature can be prevented from becoming high too much by adding and carrying out the condensation reaction of the raw material aminothiazole derivative ester after that.

[0060]However, although this method is a very effective method in the reaction of a small scale, In the reaction of an extensive scale, addition of a carboxylic acid halide compound takes a long time, The resultant (namely, reaction intermediate) of the carboxylic acid halide compound and raw material N-protection amino acid compound which were added previously is decomposed by the residual third class amine compound, and condensation yield may fall.

[0061]For this reason, in the reaction in large scales, such as an industrial scale. The method of mixing a solvent raw material N-protection amino acid, a carboxylic acid halide compound, and if needed first, adding the third class amine compound into the mixture subsequently obtained, making reaction intermediate generate, and making raw material aminothiazole derivative ester add and condense after that is preferred. According to this method, since the above problems do not arise, either, an object can be obtained with high yield.

[0062]In the method concerned, the method in particular of mixing a solvent raw material N-protection amino acid, a carboxylic acid halide compound, and if needed is not limited, but is coagulating point -100 ** of the system of reaction, and should just mix both (or three persons) suitably. What is necessary is just to determine suitably the addition conditions of the third class amine compound according to the kind and quantity of each compound to be used so that reaction temperature can maintain at coagulating point -50 ** of the system of reaction. It is preferred to stir in order to make reaction temperature uniform at the time of this time. Reaction intermediate usually generates by continuing stirring at such a temperature in about 0.1 to 40 hours.

[0063]Next, as reaction temperature when adding raw material aminothiazole derivative ester and performing a condensation reaction, Usually, although what is necessary is just to carry out below 200 ** more than the coagulating point of the system of reaction, it is preferred that it carries out temperature up to 0-80 **, and reacts further from the yield of an object and a viewpoint of the balance of reaction velocity after carrying out below -30 ** - 80 ** reacts at -30--10 ** especially. It is preferred to stir in order to make reaction temperature uniform at this time.

[0064]Although what is necessary is just to determine suitably according to the kind of reaction temperature and solvent, etc., if there is reaction time of the condensation reaction in a described method for 0.1 to as long as 40 hours, it is usually enough.

[0065]Each of each reactions in a described method can be carried out under ordinary pressure, application of pressure, or decompression. Although these reactions are feasible under atmosphere release, in order to prevent a decomposition reaction from advancing with the moisture in the atmosphere, it is preferred to carry out within the device equipped with drying tubes, such as a calcium chloride, and under inert gas atmosphere, such as nitrogen, helium, and argon.
[0066]Thus, by reacting, the amide thiazole derivative ester which has the structure according to the structure of the used raw material N-protection amino acid and raw material aminothiazole derivative ester, i.e., the amide thiazole derivative ester shown by said general formula (III), is obtained.
[0067]The obtained amide thiazole derivative ester can accept necessity, can be separated and refined, and can isolate. For example, when water and an incompatible organic solvent are used as a reactional solvent, after an acid aqueous solution, water, etc. wash the reaction mixture after ending reaction, it can carry out by drying a solvent and carrying out separation refinement by recrystallization or column chromatography.
[0068]It may use for the reaction according to a various application by making this into a starting material, without isolating the obtained reaction mixture, after carrying out suitable processing with a mixture.
[0069]
[Example]Although working example is hung up and this invention is explained still more concretely hereafter, this invention is not restricted to these working example.
[0070]After putting N-tert-carbobutoxy-L-alanine 9.46g (0.05 mol, 100%ee) and 50 ml of methylene chlorides into the reaction vessel furnished with working example 1 stirring wings, a thermometer, a nitrogen entrainment mouth, and a tap funnel and carrying out the nitrogen purge of the inside of the system of reaction to it, it cooled to -20 **. After adding 5.06 g (0.05 mol) of triethylamine to this solution, 7.73 g (0.05 mol) of o-toluoyl chloride was dropped over 20 minutes using the tap funnel. After making this slurry react at -20 ** for 2 hours, 11.46 g (0.05 mol) of 2-(2-aminothiazole 4-yl)-2-(Z)-methoxyimino ethyl acetate was added. -After making it react at 20 ** for 1 hour, temperature up was carried out to 20 ** in 20 minutes, and it reacted at the temperature for 23 hours. The place which analyzed this reaction mixture by high speed liquid chromatography (it abbreviates to HPLC henceforth.), The yield of 2-(2-N-tert-carbobutoxy-L-alanyl aminothiazole 4-yl)-2-(Z)-methoxyimino ethyl acetate (it abbreviates to BAAE henceforth.) was 84.7%. 2-(2-o-toluoyl aminothiazole 4-yl)-2-(Z)-methoxy imino acetate ester (such a by-product is henceforth abbreviated to OT object.) which is a by-product was generating 0.8%. When analyzed using the optical isolation column, the optical purity of the object was ee 99%. D object which the N-tert-carbobutoxy-L-alanine used at this time isomerized was not detected.
[0071]It was operated like working example 1 except having used the compound shown in Table 1 as working example 2 - a 10 carboxylic-acid halide compound. A result is shown in Table 1. The adduct in front expresses the reactant of carboxylic acid halide and 2-(2-aminothiazole 4-yl)-2-(Z)-methoxyimino ethyl acetate.
[0072]
[Table 1]

実施例	カルボン酸ハライド化合物	BAAE		付加体含有率 (%)
		収率 (%)	光学純度 (%ｅｅ)	
2	アセチルクロライド	８０．４	９９	１．４
3	塩化ピバロイル	８５．６	９９	０．７
4	ベンゾイルクロライド	８６．７	９９	２．４
5	１－ナフトイルクロライド	８１．８	９９	０．３
6	２－ナフトイルクロライド	８４．３	９９	０．４
7	ｍ－トルオイルクロライド	８５．４	９９	１．４
8	ｐ－トルオイルクロライド	８７．１	９９	１．８
9	ｏ－トルオイルフロライド	８２．１	９９	０．４
１０	ｏ－トルオイルブロマイド	８８．９	９９	１．６

[0073]It was operated like working example 1 except having used the compound shown in Table 2 as working example 11 - the 15 third class amine compound. A result is shown in Table 1. OT object in front shows 2-(2-o-toluoyl aminothiazole 4-yl)-2-(Z)-methoxy imino acetate ester which is a by-product.

[0074]

[Table 2]

実施例	三級アミン化合物	BAAE		OT体含有率 (%)
		収率 (%)	光学純度 (%ｅｅ)	
１１	ジイソプロピルエチルアミン	７１．０	９９	０．６
１２	Ｎ－メチルモルホリン	８７．２	９９	０．５
１３	Ｎ，Ｎ，Ｎ’，Ｎ’－テトラメチルエチレンジアミン	７８．３	９９	０．７
１４	ピリジン	７０．１	９９	１．８
１５	Ｎ，Ｎ’－ジメチルアミノピリジン	７６．４	９９	２．１

[0075]It was operated like working example 1 except having used the thing (all are ee(s) 100%) shown in Table 3 as working example 16 - a 21N-protection amino acid compound. A result is shown in Table 3.

[0076]

[Table 3]

実施例	Ｎ－保護アミノ酸化合物	生成物／収率（%）／光学純度（%ｅｅ）	OT体含有率 (%)
１６	Ｎ－アセチル－Ｌ－アラニン	２－（２－Ｎ－アセチル－Ｌ－アラニルアミノチアゾール－４－イル）－２－（Ｚ）－メトキシイミノ酢酸エチル／８１．３／９９	１．４
１７	Ｎ－ベンジルオキシカルボニル－Ｌ－アラニン	２－（２－Ｎ－ベンジルオキシカルボニル－Ｌ－アラニルアミノチアゾール－４－イル）－２－（Ｚ）－メトキシイミノ酢酸エチル／８３．９／９９	０．９
１８	Ｎ－（９－フルオレニルメトキシカルボニル）－Ｌ－アラニン	２－（２－Ｎ－（９－フルオレニルメトキシカルボニル）－Ｌ－アラニルアミノチアゾール－４－イル）－２－（Ｚ）－メトキシイミノ酢酸エチル／８４．３／９９	０．６
１９	Ｎ－トリフェニルメチル－Ｌ－アラニン	２－（２－Ｎ－トリフェニルメチル－Ｌ－アラニルアミノチアゾール－４－イル）－２－（Ｚ）－メトキシイミノ酢酸エチル／８０．６／９９	１．０
２０	Ｎ－ｔｅｒｔ－ブトキシカルボニル－Ｌ－ロイシン	２－（２－Ｎ－ｔｅｒｔ－ブトキシカルボニル－Ｌ－ロイシルアミノチアゾール－４－イル）－２－（Ｚ）－メトキシイミノ酢酸エチル／８２．４／９９	１．１
２１	Ｎ－ｔｅｒｔ－ブトキシカルボニル－Ｌ－フェニルアラニン	２－（２－Ｎ－ｔｅｒｔ－ブトキシカルボニル－Ｌ－フェニルアラニルアミノチアゾール－４－イル）－２－（Ｚ）－メトキシイミノ酢酸エチル／８４．４／９９	０．９

[0077]It was operated like working example 1 except having used the compound shown in Table 4 as working

example 22 - a 27 aminothiazole-derivative ester compound. A result is shown in Table 4. OT object in front shows the reactant of o-toluoyl chloride and an aminothiazole derivative ester compound.

[0078]

[Table 4]

実施例	アミノチアゾール誘導体エステル化合物	生成物／収率（%）／光学純度（%ｅｅ）	ＯＴ体含有率(%)
２２	２－（２－アミノチアゾール－４－イル）－２－（Ｚ）－メトキシイミノ酢酸メチル	２－（２－Ｎ－ｔｅｒｔ－ブトキシカルボニル－Ｌ－アラニルアミノチアゾール－４－イル）－２－（Ｚ）－メトキシイミノ酢酸メチル／８４．３／９９	０．７
２３	２－（２－アミノチアゾール－４－イル）－２－（Ｚ）－メトキシイミノ酢酸ベンジル	２－（２－Ｎ－ｔｅｒｔ－ブトキシカルボニル－Ｌ－アラニルアミノチアゾール－４－イル）－２－（Ｚ）－メトキシイミノ酢酸ベンジル／８５．２／９９	０．８
２４	２－（２－アミノチアゾール－４－イル）－２－（Ｚ）－エトキシイミノ酢酸エチル	２－（２－Ｎ－ｔｅｒｔ－ブトキシカルボニル－Ｌ－アラニルアミノチアゾール－４－イル）－２－（Ｚ）－エトキシイミノ酢酸エチル／８３．６／９９	０．６
２５	２－（２－アミノチアゾール－４－イル）－２－（Ｚ）－トリフェニルメトキシイミノ酢酸エチル	２－（２－Ｎ－ｔｅｒｔ－ブトキシカルボニル－Ｌ－アラニルアミノチアゾール－４－イル）－２－（Ｚ）－トリフェニルメトキシイミノ酢酸エチル／８６．１／９９	１．１
２６	２－（２－アミノチアゾール－４－イル）酢酸エチル	２－（２－Ｎ－ｔｅｒｔ－ブトキシカルボニル－Ｌ－アラニルアミノチアゾール－４－イル）酢酸エチル／８４．５／９９	０．８
２７	２－（２－アミノチアゾール－４－イル）－２－ペンテン酸エチル	２－（２－Ｎ－ｔｅｒｔ－ブトキシカルボニル－Ｌ－アラニルアミノチアゾール－４－イル）－２－ペンテン酸エチル／８５．９／９９	０．９

[0079]After putting N-tert-carbobutoxy-L-alanine 9.46g (0.05 mol, 100%ee) and 50 ml of methylene chlorides into the reaction vessel furnished with working example 28 stirring wings, a thermometer, a nitrogen entrainment mouth, and a tap funnel and carrying out the nitrogen purge of the inside of the system of reaction to it, it cooled to -20 **. After adding 7.73 g (0.05 mol) of o-toluoyl chloride to this solution, 5.06 g (0.05 mol) of triethylamine was dropped over 20 minutes using the tap funnel. After making this slurry react at -20 ** for 2 hours, 11.46 g (0.05 mol) of 2-(2-aminothiazole 4-yl)-2-(Z)-methoxyimino ethyl acetate was added. -After making it react at 20 ** for 1 hour, temperature up was carried out to 20 ** in 20 minutes, and it reacted at the temperature for 23 hours. The yield of BAAE was 85.3% when this reaction mixture was analyzed by HPLC. 2-(2-o-toluoyl aminothiazole 4-yl)-2-(Z)-methoxy imino acetate ester (OT object) which is a by-product was generating 0.4%. When analyzed using the optical isolation column, the optical purity of the object was ee 99%. D object which the N-tert-carbobutoxy-L-alanine used at this time isomerized was not detected.

[0080]It was operated like working example 1 except having used the compound shown in Table 5 as 29 to working example 31 reactional solvent. A result is shown in Table 5.

[0081]

[Table 5]

実施例	反応溶媒	BAAE		ＯＴ体含有率(%)
		収率（%）	光学純度(%ｅｅ)	
２９	テトラヒドロフラン	８７．２	９９	０．５
３０	酢酸エチル	８６．７	９９	０．７
３１	トルエン	８２．１	９９	０．４

[0082]After putting N-tert-carbobutoxy-L-alanine 9.46g (0.05 mol, 100%ee) and 50 ml of methylene chlorides into the reaction vessel furnished with comparative example 1 stirring wings, a thermometer, a nitrogen

entrainment mouth, and a tap funnel and making it dissolve in it, it cooled to 5 **. Dicyclohexylcarbodiimide was added, after adding 11.46 g (0.05 mol) of 2-(2-aminothiazole 4-yl)-2-(Z)-methoxyimino ethyl acetate, and 0.61 g (0.005 mol) of N,N'-dimethylamino pyridine to this solution and making it stir uniformly. After making it react at 5 ** for 0.5 hour, temperature up was carried out to 20 ** in 20 minutes, and it reacted at the temperature for 23 hours. The yield of BAAE was 67.0% when this reaction mixture was analyzed by HPLC. The N-tert-carbobutoxy-L-alanine anhydride of the by-product was generating 32.5%.

[0083]The N-tert-carbobutoxy-L-alanine anhydride 3.60g (0.01 mol) was added to 2100 ml of comparative example eggplant type flask, and 20 ml of methylene chlorides were dissolved in it. 2.29 g (0.01 mol) of 2-(2-aminothiazole 4-yl)-2-(Z)-methoxyimino ethyl acetate and 0.12 g (0.001 mol) of N,N'-dimethylamino pyridine were added to this solution, and it was made to react for four days at 25 **. When this reaction mixture was analyzed by HPLC, the yield of BAAE is only 4.3% and it was checked that the reactivity of the acid anhydride of N-protection amino acid compound and an aminothiazole derivative ester compound is low.

[0084]The result of the comparative examples 1 and 2 shows that there is a reaction path which goes via the acid anhydride of N-protection amino acid compound as one of the reaction paths, and yield is low since the reaction of this acid anhydride and an aminothiazole derivative ester compound is very slow, when a carbodiimide system condensing agent is used.

[0085]After putting N-tert-carbobutoxy-L-alanine 9.46g (0.05 mol, 100%ee) and 50 ml of methylene chlorides into the reaction vessel furnished with comparative example 3 stirring wings, a thermometer, a nitrogen entrainment mouth, and a tap funnel and carrying out the nitrogen purge of the inside of the system of reaction to it, it cooled to -20 **. After adding 3.56 g (0.05 mol) of pyrrolidine to this solution, 7.73 g (0.05 mol) of o-toluoyl chloride was dropped over 20 minutes using the tap funnel. After making this slurry react at -20 ** for 2 hours, 11.46 g (0.05 mol) of 2-(2-aminothiazole 4-yl)-2-(Z)-methoxyimino ethyl acetate was added. -After making it react at 20 ** for 1 hour, temperature up was carried out to 20 ** in 20 minutes, and it reacted at the temperature for 23 hours. When this reaction mixture is analyzed by HPLC, the yield of 2-(2-N-tert-carbobutoxy-L-alanyl aminothiazole 4-yl)-2-(Z)-methoxyimino ethyl acetate (BAAE) is only 12.3%, N-tert-carbobutoxy-pyrrolidine was detected 69.8%.

[0086]If it changes to the third class amine compound and the first class or the second class amine compound is used even when a carboxylic acid halide compound is used as shown in the comparative example 3, the by-product to which raw material amino acid, the first class, or the second class amine compound reacted will carry out a byproduction, and yield will fall.

[0087]After putting N-tert-carbobutoxy-L-alanine 9.46g (0.05 mol, 100%ee) and 50 ml of methylene chlorides into the reaction vessel furnished with comparative example 4 stirring wings, a thermometer, a nitrogen entrainment mouth, and a tap funnel and carrying out the nitrogen purge of the inside of the system of reaction to it, it cooled to -20 **. The tap funnel was used for this and 7.73 g (0.05 mol) of o-toluoyl chloride was dropped at it over 20 minutes. After making this slurry react at -20 ** for 2 hours, 11.46 g (0.05 mol) of 2-(2-aminothiazole 4-yl)-2-(Z)-methoxyimino ethyl acetate was added. -After making it react at 20 ** for 1 hour, temperature up was carried out to 20 ** in 20 minutes, and it reacted at the temperature for 23 hours. When this reaction mixture is analyzed by HPLC, the yield of 2-(2-N-tert-carbobutoxy-L-alanyl aminothiazole 4-yl)-2-(Z)-methoxyimino ethyl acetate (BAAE) is only 57.4%, The 2-(L-alanyl aminothiazole 4-yl)-2-(Z)-methoxyimino ethyl acetate from which the N-tert-butoxycarbonyl group was desorbed from BAAE 2.3%, The 2-(2-N-tert-carbobutoxy-L-alanyl aminothiazole 4-yl)-2-(E)-methoxyimino ethyl acetate which raw material aminothiazole

derivative ester isomerized was detected 0.6%.

[0088]Yield is low in not using it combining the third class amine compound, as shown in the comparative example 4. It not only cannot obtain an object with high optical purity with high yield, but raw material aminothiazole derivative ester isomerizes and it becomes difficult [reuse of an unreacted raw material].

[0089]

[Effect of the Invention]According to the manufacturing method of this invention, the amide thiazole derivative ester compound which is an important intermediate of a prodrug TAPUI cephalosporin derivative can be obtained from raw material N-protection amino acid and raw material aminothiazole derivative ester with high yield. The amide thiazole derivative ester compound obtained in this invention can maintain the high optical purity of the raw material aminothiazole derivative ester used as a raw material. Drug effect can say that it is the process outstanding as a manufacturing method of a greatly different medicine intermediate according to the kind of optical isomer.

[Translation done.]